Endotoxin Shock With Massive Adrenal Hemorrhage

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WATERHOUSE,[17] an English physician, in 1911 described the syndrome of adrenal apoplexy in an infant who died with fever and purpura. In 1918 Friderichsen,[4] a Copenhagen pediatrician, described several similar cases and related them to meningococcemia. Since then, cases have been reported in which adrenal hemorrhage has occurred in the course of other infections.

During the past ten years there has been great interest in the endotoxins of Gram-negative bacteria and their relation to the pathogenesis of shock. A vast body of literature* has accumulated on the source, the chemical nature and the pathophysiologic features of endotoxin. However, the reports of adrenal hemorrhage in association with endotoxin shock are relatively scant. In a recent review Spink[12] emphasized the rarity of this association. The present report is of a case of massive bilateral adrenal hemorrhage which occurred during the course of Gram-negative septicemia and shock. Related to the report is a discussion of the properties of endotoxin as related to the pathogenesis of adrenal hemorrhage.

Report of a Case

The patient was a 38-year-old white man who was admitted to hospital for relapse of pemphigus vegetans for which he had been treated at the time of first diagnosis, confirmed by biopsy, some two years previously. Treatment with steroids and ACTH intermittently had given fair results. Until that illness he apparently had been in good health.

At the time of admittance because of relapse, the blood pressure was 160/110 mm of mercury. Except for numerous bullous and crusted skin lesions on the face, head and upper extremities, no abnormalities were noted on physical examination.

Prednisone and ACTH were given and the lesions gradually improved. Six weeks after admission, massive gastrointestinal hemorrhage occurred and a subtotal gastrectomy was performed. Two weeks later there was dehiscence of the wound, which was repaired. One week later, the temperature suddenly rose to 104°F. Shaking chills developed and the blood pressure fell to 70/50 mm. Despite vigorous treatment with antibiotics, vasopressors and large doses of steroids, the patient died the next day, nine weeks after admission.

At autopsy, the body was that of a well developed, well nourished man with numerous dried, crusted skin lesions. The surgical incision communicated with the peritoneal cavity where several necrotic and purulent areas were noted. Shock and septicemia were manifested by acute splenitis, "shock kidneys," fatty metamorphosis of the liver and subendocardial hemorrhage. The adrenal glands were so filled with clotted blood that only a rim of cortex could be seen (Figure 1). Microscopically, only a few layers of cortical cells were seen as the adrenal glands were almost entirely replaced by areas of necrosis and thrombus. Blood cultures and cultures of the surgical wound yielded Escherichia coli.

Discussion

The changes in the adrenal glands in the presence of pemphigus must be considered before discussing the relationship of endotoxin shock to adrenal hemorrhage. In 1953, Lever[6] reviewed the autopsy reports on all cases of pemphigus from Massachusetts General Hospital and found notation of

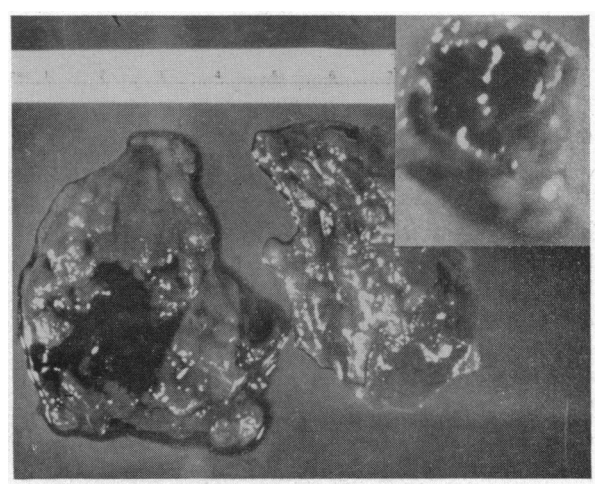

Figure 1.—Adrenal glands almost completely filled with clotted blood. Cross-section (inset) shows only a rim of cortex remaining.

*References Nos. 1, 5, 8, 9, 10, 11, 14, 15, 18.

This study was accomplished at the University of Illinois Research and Educational Hospital, Chicago.

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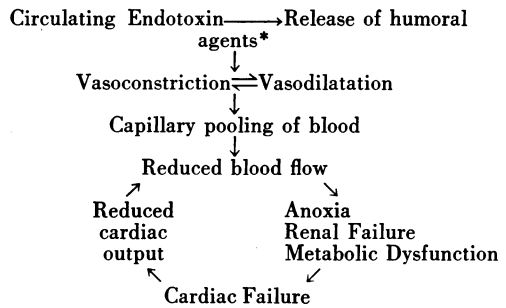
changes in the adrenal glands in about one-third. However, the changes consisted of small, isolated areas of necrosis, unlike the massive hemorrhagic necrosis in the present case.

The endotoxins of Gram-negative bacteria have been shown to possess many interesting properties, some of them having a bearing on the present case. In endotoxin shock, the basic physiologic disturbance is severe vasoconstriction followed by or alternating with vasodilatation and venous pooling of blood. The mechanism by which these events take place is not entirely clear. The effect is evidently vascular. However, if endotoxin is applied directly to the blood vessel walls, there is no reaction. Weil and coworkers[18] showed that vascular changes can be produced in the isolated perfused dog lung only when the perfusate was plasma or blood from an animal pretreated with endotoxin. This experiment leads to the postulation of a mediator or "trigger" substance to explain the effects of endotoxin. During the early phases of experimental endotoxin shock, there are elevated levels of serotonin, epinephrine, norepinephrine and histamine in the blood. The generalized hemodynamic reactions are summarized in the accompanying diagram.



Once capillary pooling of blood and reduced flow of blood occur, a vicious cycle is established, leading to anoxia, to renal failure and to cardiac failure, which in turn reduces the cardiac output and further reduces blood flow.

These effects also operate at the tissue level. Thomas[15] showed that in rabbits pretreated with endotoxin skin necrosis developed at the site of minute intradermal injections of epinephrine. In his study, progressive changes in vascular reactivity to epinephrine were noted, with initial hyper-reactivity followed by vasodilatation. This effect may be blocked by pretreatment with adrenergic blocking agents. In light of these reactions to epinephrine in the presence of endotoxin and because this reaction occurs primarily in tissues with the highest epinephrine content, it has been postulated that adrenal hemorrhagic necrosis is a direct manifestation of a target site reaction.[13]

*Epinephrine, serotonin, histamine, etc.

Another interesting property of endotoxin is the production of the Shwartzman reaction described first in the late 1920's. Dermal hemorrhagic necrosis, the characteristic lesion of the phenomenon, is brought about by an initial intradermal injection of endotoxin followed in 18 to 24 hours by a provoking dose given intravenously. Shortly thereafter, hemorrhagic necrosis is noted at the initially prepared site. If both doses are given intravenously, a generalized reaction is induced, characterized by the presence of bilateral renal cortical necrosis. Pretreatment with cortisone or the administration of a reticuloendothelial blocking agent sets the stage for the generalized reaction so that only one dose of endotoxin is required.[10] In animals subjected to the generalized reaction, hemorrhagic necrosis of the kidneys, heart, spleen, liver, adrenal glands, lungs and brain is noted at autopsy. Although not all the typical pathologic findings were present in the case herein reported, one still must consider this reaction as a possible factor in the pathogenesis of the adrenal hemorrhage. This is especially true in light of the prolonged corticosteroid treatment.

One other important factor is the effect of stress which would certainly be present under the conditions of endotoxemia. It has been postulated that conditions of stress cause liberation of epinephrine which stimulates the pituitary gland to excrete increased amounts of ACTH which in turn produces irreversible effects on the adrenal glandular epithelium. These changes are more subtle than those found in the case herein presented; therefore, stress is probably a small factor in the production of adrenal hemorrhage, if related at all.

Summary

A case of pemphigus is presented in which endotoxin shock and massive adrenal hemorrhage resulted. Although endotoxin shock is not commonly accompanied by adrenal hemorrhage, this association should be considered in the clinical evaluation and represents a definite indication for adrenal steroid therapy.

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